NKR 13 Alkoholbehandling: Acamprosat for alcohol dependence

Review information

Authors

Sundhedsstyrelsen[1]

[1][Empty affiliation]

Citation example: S. NKR 13 Alkoholbehandling: Acamprosat for alcohol dependence. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Contact person

[Empty name]

Characteristics of studies

Characteristics of included studies

Anton 2006

Methods	
Participants	
Interventions	
Outcomes	
Notes	For more information see "Rösner S, Hackl-Herrwerth A, Leucht S, Lehert P, Vecchi S, Soyka M. Acamprosate for alcohol dependence. Cochrane Database of Systematic Reviews 2010, Issue 9. Art. No.: CD004332. DOI: 10.1002/14651858.CD004332.pub2."

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Berger 2013

Methods	RCT12 weeks
Participants	alcohol dependent with 2 episodes of heavy drinking(≥ 5 standard drinks per drinking day for men/≥ 4 for women) each week, patients with treated depression or anxiety and stable pharmacotherapy for at least 1 months were not excluded, but major psychiatric conditions (bipolar, suicidal ideation or beahviour, history of suicide attempts, any other substance abuse other than alcohol or nicotine, and patients needing more intensive treatments for alcohol dependence (e.g. history of alcohol withdrawal seizures or delirium tremens)) were excluded.
Interventions	acamprosat
Outcomes	drop-out due to all reasons after 12 weeks, percent days abstinent (PDA) posttreatment (12 weeks)
Notes	USA, funding: investigator-initiated grant from Forest Research Institute. The acamprosate medication was provided by Forest institute

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	p670: "statisticians at each site generated a computerized numbered, random allocation sequence that was implemented by correspondingly numbered blister packs"
Allocation concealment (selection bias)	Low risk	p670:" the statisticians concealed the sequence until the last participant completed the study".
Blinding of participants and personnel (performance bias)	Low risk	p670:" the statisticians concealed the sequence until the last participant completed the study"; p670 methods section : "matching placebo"
Blinding of outcome assessment (detection bias)	Low risk	p670:" the statisticians concealed the sequence until the last participant completed the study".
Incomplete outcome data (attrition bias)	Unclear risk	p669: There is a flowchart of patients at various stages of the trial, including details of those who were lost to follow up. P670 data analysis section states "Due to minimal missing data, with the eception of the TLFB measure due to some participant drop out, no data imputations were performed" - however, it was unclear what number of patients were actually included in the analysis.
Selective reporting (reporting bias)	Unclear risk	We do not have the protocol.
Other bias	Low risk	no other types of bias noted

Chick2000

Methods	
Participants	
Interventions	
Outcomes	
Notes	For more information see "Rösner S, Hackl-Herrwerth A, Leucht S, Lehert P, Vecchi S, Soyka M. Acamprosate for alcohol dependence. Cochrane Database of Systematic Reviews 2010, Issue 9. Art. No.: CD004332. DOI: 10.1002/14651858.CD004332.pub2."

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Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Geerlings 1997

Methods	
Participants	
Interventions	
Outcomes	
Notes	For more information see "Rösner S, Hackl-Herrwerth A, Leucht S, Lehert P, Vecchi S, Soyka M. Acamprosate for alcohol dependence. Cochrane Database of Systematic Reviews 2010, Issue 9. Art. No.: CD004332. DOI: 10.1002/14651858.CD004332.pub2."

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Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Higuchi 2015

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Overall ● *164 fik placebo og 163 acamprosat*: **Included criteria:** Those who (1) met the diagnostic guidelines of dependencesyndromespecified in ICD-10 and were diagnosed with alcohol dependence, (2) were willing to remain abstinent, (3) were 20 years or older,(4) had a fixed address, and (5) could have constant contact with the medical institution during the clinical study period **Excluded criteria:** Those who (1) had a history of use of stimulants, cannabis, ornarcotics (excluding therapeutic use);(2) had a history of abuse of psychotropic drugs, organicsolvents, or antipyretic / analgesic / antiphlogistic drugs; (3) also suffered from a psychiatric disorder requiring treatment withantidepressants, antipsychoticdrugs,

	antiepilepticdrugs, or antimanic drugs; (4) had epilepsy;(5)hadahistoryofattemptedsuicide;(6)alsosueredfromaseriousrenaldisorderorhepatopathy;(7) had undergone intestinal resection; (8) had chronic pancreatitis; or (9) had been admitted toa transitional facility **Pretreatment:** flere i placebo gruppe med tidl inpatient treatment og kendt delirium tremens
Interventions	**Intervention Characteristics** Intervention ● *Description*: Peroral acamprosat ● *Duration (weeks)*: 24 ● *Dose*: 1998 mg / dag, fordelt på 3 doser ● *Follow-up time: 24 weeks*: ● *acamprosat 333 mg x 3 daglig + psykoterapi, der var forskellig i de forskellige institutioner*: Control ● *Description*: Placebo ● *Duration (weeks): 24* ● F*ollow-up time: 24 weeks*: ● *acamprosat 333 mg x 3 daglig + psykoterapi, der var forskellig i de forskellige institutioner*:
Outcomes	*Frafald af alle årsager* ● **Outcome type**: DichotomousOutcome ● **Reporting**: Fully reported ● **Direction**: Lower is better ● **Data value**: Endpoint *Andel afholdende* ● **Outcome type**: DichotomousOutcome ● **Reporting**: Fully reported ● **Direction**: Higher is better ● **Data value**: Endpoint *Frafald pga. bivirkninger* ● **Outcome type**: DichotomousOutcome ● **Reporting**: Fully reported ● **Direction**: Lower is better ● **Data value**: Endpoint *Gastrointestinale bivirkninger (diarre)* ● **Outcome type**: DichotomousOutcome ● **Reporting**: Fully reported ● **Direction**: Lower is better ● **Data value**: Endpoint
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "An independent investigational drug allocation controller, who was affiliated neither with a participating medical institution nor with the sponsor, carried out blinding of the investigational drugs."
Allocation concealment (selection bias)	Low risk	Quote: "The investigators remained blinded to the group allocation of those who dropped out throughout the study." Judgement Comment: The drug was handed out in numerical order, making patient or investigator awaraness of which was drug and vice versa unlikely.

Blinding of participants and personnel (performance bias)	Low risk	Judgement Comment: SInce, the intervention was a drug with a vague mode of action, which the patients had little knowledge of , it seems likely that patients were unaware of whether they received placebo or campral.
Blinding of outcome assessment (detection bias)	Low risk	Judgement Comment: Since the investigators were blinded throughout the study
Incomplete outcome data (attrition bias)	Low risk	Quote: "and his/ her cooperative attendant. In ambiguous cases, subjects were assumed to have consumed alcohol. Days for which a missing value was detected and days on which it was unknown if the subject drank"
Selective reporting (reporting bias)	Unclear risk	Judgement Comment: der er ingen study protocol
Other bias	High risk	Judgement Comment: Kilder til bias: Patienterne skulle have en adresse, måtte ikke have andet misbrug, måtte ikke have psykiatrisk comorbidity, måtte ikke være lever, nyre eller pancreas syge. Det snævrer patientpopulationene ind.

Kiefer2003

Methods	
Participants	
Interventions	incl cognitive therapy
Outcomes	
Notes	For more information see "Rösner S, Hackl-Herrwerth A, Leucht S, Lehert P, Vecchi S, Soyka M. Acamprosate for alcohol dependence. Cochrane Database of Systematic Reviews 2010, Issue 9. Art. No.: CD004332. DOI: 10.1002/14651858.CD004332.pub2."

Risk of bias table

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Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Mann2013

Methods	RCT12 weeks
Participants	alcohol dependent, admitted for alcohol detoxification, no major psychiatric illness
Interventions	acamprosat
Outcomes	drop-out due to all reasons (relapse to heavy drinking - not relevant to NKR)
Notes	Germany, Federal Government of Germany + medication donated by Bristol Meyer Squibb and MERCK Serono

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The sequence generation not described in protocol either: Mann et al., 2009 ("Searching for Responders to Acamprosate and Naltrexone in Alcoholism Treatment: Rationale and Design of the Predict Study") states "For allocating these patients to the 3 treatment arms, an imbalanced randomization algorithm is used ensuring proportions of 2:2:1 between acamprosate, naltrexone, and placebo, respectively." It is unclear how this was done and by whom.
Allocation concealment (selection bias)	Unclear risk	p681 of Mann et al., 2009 ("Searching for Responders to Acamprosate and Naltrexone in Alcoholism Treatment: Rationale and Design of the Predict Study") states "For allocating these patients to the 3 treatment arms, an imbalanced randomization algorithm is used ensuring proportions of 2:2:1 between acamprosate, naltrexone, and placebo, respectively." It is unclear how this was done and by whom.
Blinding of participants and personnel (performance bias)	Low risk	p 939-940: "To ensure double-blind treatment, each patient had to take seven pills daily (three in the morning, tow at noon and two in the late afternoon), regardless of the drug they were taking. Each blister pack contained a 1-week supply of medication". There was no information in the text to state whether the tablets for both active treatments and for placebo all look identical - but I presume they did. The protocol (Mann et al., 2009 -Searching for Responders to Acamprosate and Naltrexone in Alcoholism Treatment: Rationale and Design of the Predict Study) does not provide any further details.
Blinding of outcome assessment (detection bias)	Unclear risk	There were no details in the actual paper and no further details in the protocol
Incomplete outcome data (attrition bias)	Low risk	Figure 1 clearly states number of patients who discontinued, and the number of patients that were included in the analyses. The number of patients included in the analyses in figure 1 agrees with data in table 1
Selective reporting (reporting bias)	Low risk	Primary outcome and primary efficacy analysis are same in protocol and paper.
Other bias	Low risk	no other bias noted

Morley2006

Methods	
Participants	
Interventions	
Outcomes	
Notes	For more information see "Rösner S, Hackl-Herrwerth A, Leucht S, Lehert P, Vecchi S, Soyka M. Acamprosate for alcohol dependence. Cochrane Database of Systematic Reviews 2010, Issue 9. Art. No.: CD004332. DOI: 10.1002/14651858.CD004332.pub2."

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Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Namkoong2003

Methods	
Participants	
Interventions	
Outcomes	
Notes	For more information see "Rösner S, Hackl-Herrwerth A, Leucht S, Lehert P, Vecchi S, Soyka M. Acamprosate for alcohol dependence. Cochrane Database of Systematic Reviews 2010, Issue 9. Art. No.: CD004332. DOI: 10.1002/14651858.CD004332.pub2."

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Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Paille1995

Methods	
Participants	
Interventions	
Outcomes	
Notes	For more information see "Rösner S, Hackl-Herrwerth A, Leucht S, Lehert P, Vecchi S, Soyka M. Acamprosate for alcohol dependence. Cochrane Database of Systematic Reviews 2010, Issue 9. Art. No.: CD004332. DOI: 10.1002/14651858.CD004332.pub2."

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Incomplete outcome data (attrition bias)	Unclear risk	

Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Pelc 1997 2g/day

Methods	
Participants	
Interventions	
Outcomes	
Notes	For more information see "Rösner S, Hackl-Herrwerth A, Leucht S, Lehert P, Vecchi S, Soyka M. Acamprosate for alcohol dependence. Cochrane Database of Systematic Reviews 2010, Issue 9. Art. No.: CD004332. DOI: 10.1002/14651858.CD004332.pub2."

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Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Poldrugo1997

Methods	
Participants	
Interventions	
Outcomes	
Notes	For more information see "Rösner S, Hackl-Herrwerth A, Leucht S, Lehert P, Vecchi S, Soyka M. Acamprosate for alcohol dependence. Cochrane Database of Systematic Reviews 2010, Issue 9. Art. No.: CD004332. DOI: 10.1002/14651858.CD004332.pub2."

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Blinding of participants and personnel (performance bias)	Unclear risk	

Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Sass1996

Methods	
Participants	
Interventions	incl cognitive therapy
Outcomes	
Notes	For more information see "Rösner S, Hackl-Herrwerth A, Leucht S, Lehert P, Vecchi S, Soyka M. Acamprosate for alcohol dependence. Cochrane Database of Systematic Reviews 2010, Issue 9. Art. No.: CD004332. DOI: 10.1002/14651858.CD004332.pub2."

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Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Tempesta2000

Methods	
Participants	
Interventions	incl cognitive therapy
Outcomes	
Notes	For more information see "Rösner S, Hackl-Herrwerth A, Leucht S, Lehert P, Vecchi S, Soyka M. Acamprosate for alcohol dependence. Cochrane Database of Systematic Reviews 2010, Issue 9. Art. No.: CD004332. DOI: 10.1002/14651858.CD004332.pub2."

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Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Withwoth1996

Methods	
Participants	
Interventions	
Outcomes	
Notes	For more information see "Rösner S, Hackl-Herrwerth A, Leucht S, Lehert P, Vecchi S, Soyka M. Acamprosate for alcohol dependence. Cochrane Database of Systematic Reviews 2010, Issue 9. Art. No.: CD004332. DOI: 10.1002/14651858.CD004332.pub2."

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Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Wölver 2011

Methods	RCT 6 months
Participants	After inpatient detoxification, alcohol dependence, no major psychiatry
Interventions	acamprosat
Outcomes	drop-out due to all reasons (other outcomes not relevant for NKR)
Notes	Germany, German Federal Ministry of Education and Research, medication was provided by Merck Lipha

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear how sequence was generated, although the process was carried out by an independent external centre
Allocation concealment (selection bias)	Low risk	p418: process was carried out by an independent external centre
Blinding of participants and personnel (performance bias)	Low risk	No details if placebo and active treatment were identical ornot, but we think it was
Blinding of outcome assessment (detection bias)	Unclear risk	No details provided in paper
Incomplete outcome data (attrition bias)	Low risk	p419: Analysis was performed on intention-to-treat; p421, footnote to figure 4: number of patients included in analysis at 6 months, and 6 months post treatment was intention-to-treat and included all randomised patients.
Selective reporting (reporting bias)	High risk	We do not have the protocol, but miss outcome data on abstinence alone instead of abstinence+improvement.
Other bias	Low risk	No other types of bias noted

Footnotes

Characteristics of excluded studies

Donoghue 2015

Reason for exclusion	Wrong study design

Jonas 2014

Reason for exclusion	Wrong study design

Palpacuer 2017

Reason for exclusion	Wrong study design

Takimura 2015

Reason for exclusion	Dublicate

Footnotes

Characteristics of studies awaiting classification

Footnotes

Characteristics of ongoing studies

Footnotes

References to studies

Included studies

Anton 2006

[Empty]

Berger 2013

[Empty]

Chick2000

[Empty]

Geerlings 1997

[Empty]

Higuchi 2015

Higuchi, Susumu; Japanese Acamprosate Study Group. Efficacy of acamprosate for the treatment of alcohol dependence long after recovery from withdrawal syndrome: a randomized, double-blind, placebo-controlled study conducted in Japan (Sunrise Study).. Journal of Clinical Psychiatry 2015;76(2):181-188. [DOI:]

Kiefer2003

[Empty]

Mann2013

[Empty]

Morley2006

[Empty]

Namkoong2003

[Empty]

Paille1995

[Empty]

Pelc 1997 2g/day

[Empty]

Poldrugo1997

[Empty]

Sass1996

[Empty]

Tempesta2000

[Empty]

Withwoth1996

[Empty]

Wölver 2011

[Empty]

Excluded studies

Donoghue 2015

Donoghue, Kim; Elzerbi, Catherine; Saunders, Rob; Whittington, Craig; Pilling, Stephen; Drummond, Colin. The efficacy of acamprosate and naltrexone in the treatment of alcohol dependence, Europe versus the rest of the world: a meta-analysis. Addiction 2015;110(6):920-930. [DOI:]

Jonas 2014

Jonas, Daniel E.; Amick, Halle R.; Feltner, Cynthia; Bobashev, Georgiy; Thomas, Kathleen; Wines, Roberta; Kim, Mimi M.; Shanahan, Ellen; Gass, C. Elizabeth; Rowe, Cassandra J.; Garbutt, James C.. Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis. JAMA 2014;311(18):1889-1900. [DOI:]

Palpacuer 2017

Palpacuer, Clement; Duprez, Renan; Huneau, Alexandre; Locher, Clara; Boussageon, Remy; Laviolle, Bruno; Naudet, Florian. Pharmacologically controlled drinking in the treatment of alcohol dependence or alcohol use disorders: a systematic review with direct and network meta-analyses on nalmefene, naltrexone, acamprosate, baclofen and topiramate. Addiction 2017;(Journal Article). [DOI:]

Takimura 2015

Takimura T.; Higuchi, S.. Efficacy of acamprosate for the treatment of alcohol dependence and predictors of response: An RCT conducted in Japan.. Alcoholism: Clinical and Experimental Research.Conference: 38th Annual Scientific Meeting of the Research Society on Alcoholism.San Antonio, TX United States.Conference Publication: (var.pagings) 2015;39(Journal Article):295A. [DOI:]

Other references

Additional references

Other published versions of this review

Classification pending references

Data and analyses

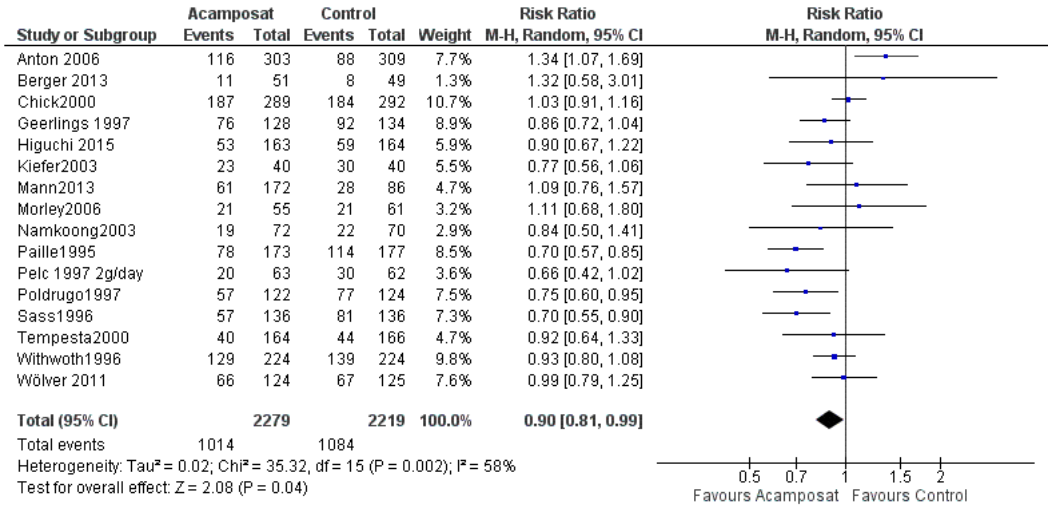
1 acamprosat versus placebo

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.2 Dropout all reasons	16	4498	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.81, 0.99]
1.7 Drinks per drinking day, at 3 month	2	258	Mean Difference (IV, Random, 95% CI)	-0.17 [-1.99, 1.65]
1.8 Adverse events (diarrhea) EoT	12	3415	Risk Ratio (M-H, Random, 95% CI)	1.71 [1.33, 2.19]
1.9 Adverse events (nausea) EoT	4	908	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.86, 1.51]
1.10 Drop-out due to adverse events (EoT)	15	4500	Risk Ratio (M-H, Random, 95% CI)	1.51 [0.81, 2.79]
1.11 Seriuos adverse events (EoT)	4	908	Risk Ratio (M-H, Random, 95% CI)	1.60 [0.36, 7.14]
1.12 Percent days abstinent at 6-12 month after baseline	1	612	Mean Difference (IV, Random, 95% CI)	-0.07 [-4.19, 4.06]

1.13 Number of patients lapsed 6-12 month after baseline	11	3226	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.77, 0.90]
1.14 Number of patients lapsed 3 month after baseline	3	546	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.86, 1.00]
1.15 Number of patients lapsed 6-12 month FU	1	448	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.87, 0.98]

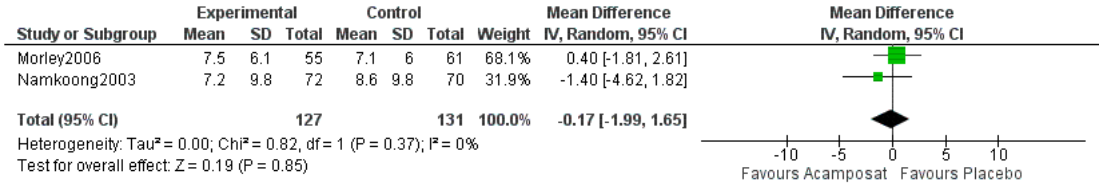
Figures

Figure 1 (Analysis 1.2)



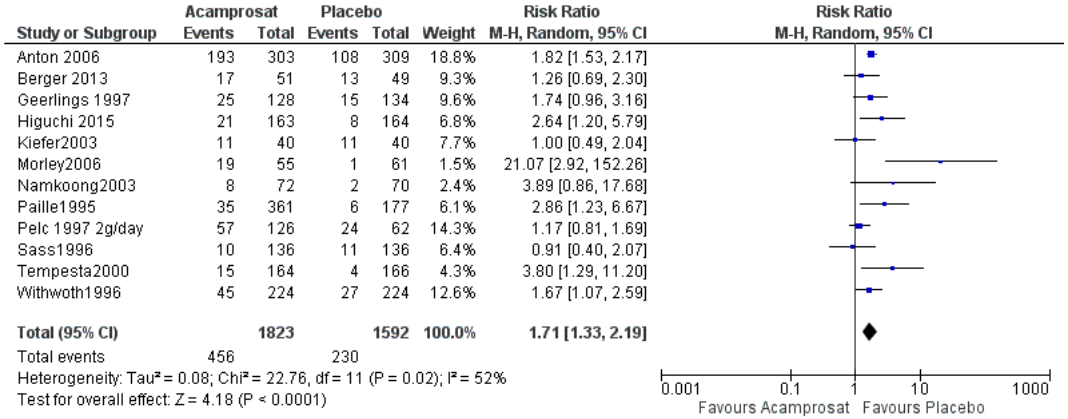
Forest plot of comparison: 1 acamprosat versus placebo, outcome: 1.2 Dropout all reasons.

Figure 2 (Analysis 1.7)



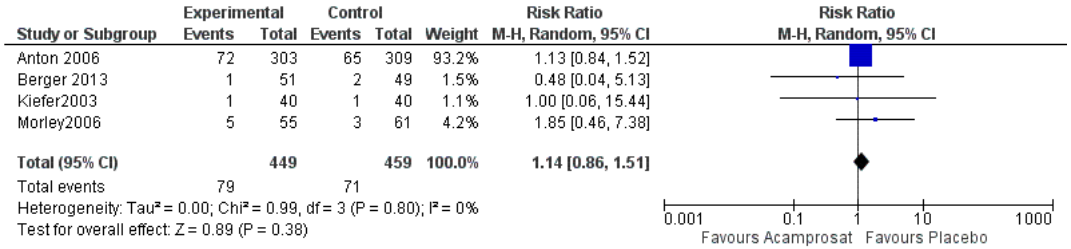
Forest plot of comparison: 1 acamprosat versus placebo, outcome: 1.7 Drinks per drinking day, at 3 month.

Figure 3 (Analysis 1.8)



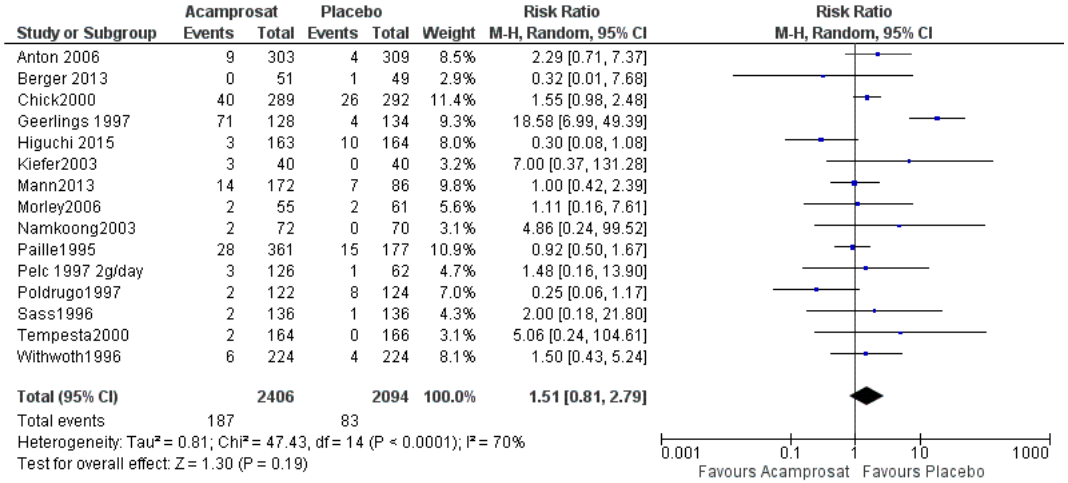
Forest plot of comparison: 1 acamprosat versus placebo, outcome: 1.8 Adverse events (diarrhea) EoT.

Figure 4 (Analysis 1.9)



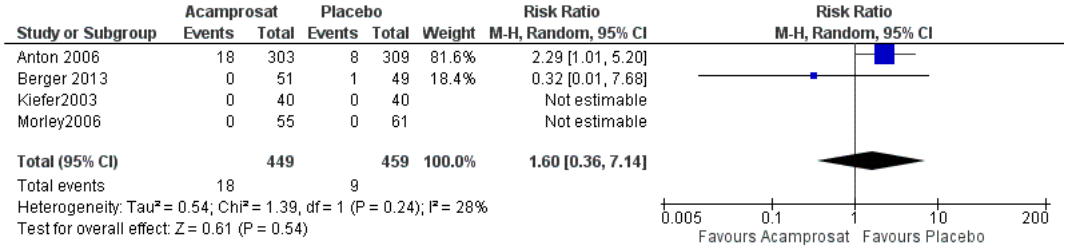
Forest plot of comparison: 1 acamprosat versus placebo, outcome: 1.9 Adverse events (nausea) EoT.

Figure 5 (Analysis 1.10)



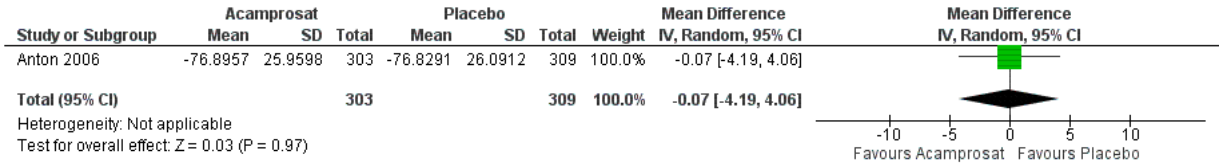
Forest plot of comparison: 1 acamprosat versus placebo, outcome: 1.10 Drop-out due to adverse events (EoT).

Figure 6 (Analysis 1.11)



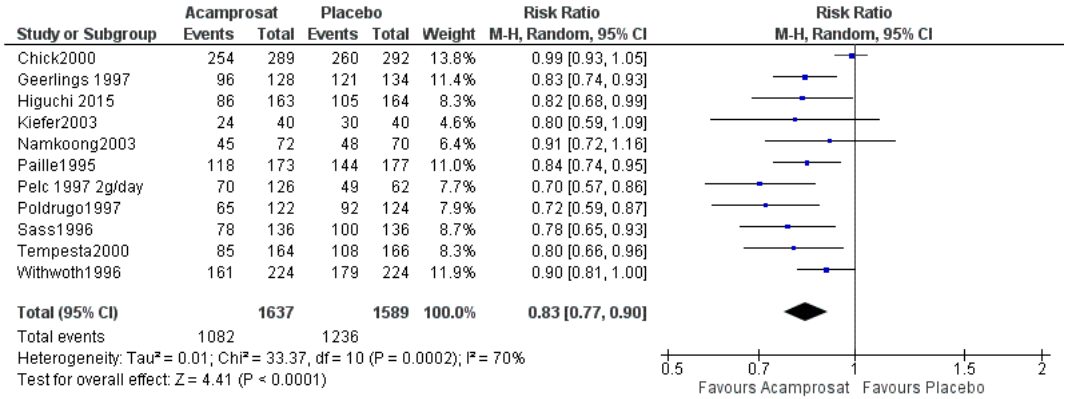
Forest plot of comparison: 1 acamprosat versus placebo, outcome: 1.11 Seriuos adverse events (EoT).

Figure 7 (Analysis 1.12)



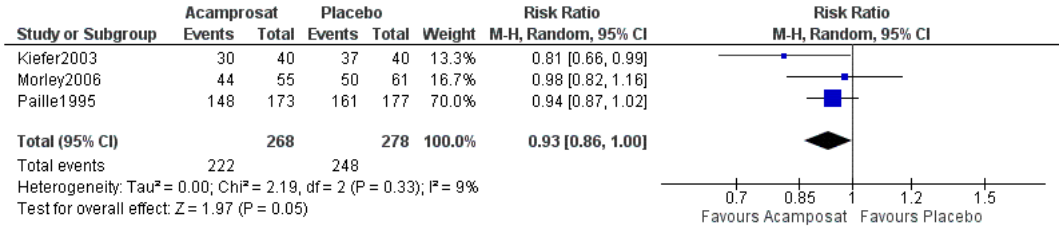
Forest plot of comparison: 1 acamprosat versus placebo, outcome: 1.12 Percent days abstinent at 6-12 month after baseline.

Figure 8 (Analysis 1.13)



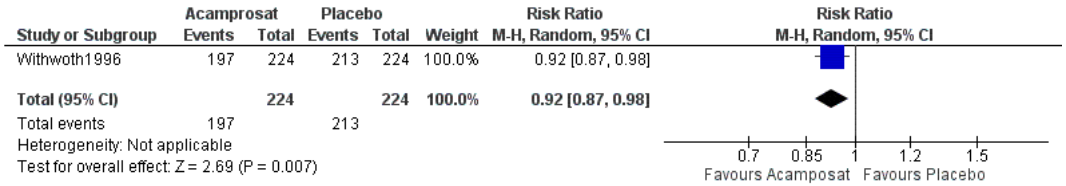
Forest plot of comparison: 1 acamprosat versus placebo, outcome: 1.13 Number of patients lapsed 6-12 month after baseline.

Figure 9 (Analysis 1.14)



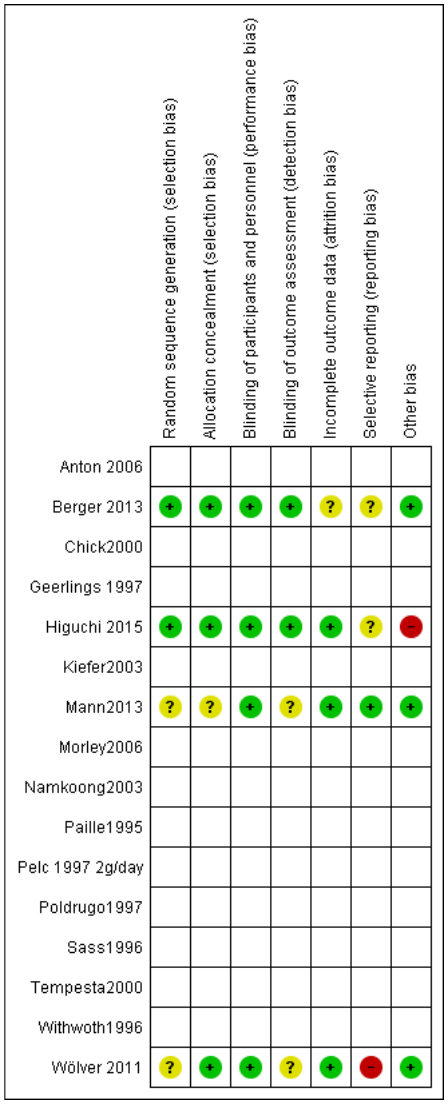
Forest plot of comparison: 1 acamprosat versus placebo, outcome: 1.14 Number of patients lapsed 3 month after baseline.

Figure 10 (Analysis 1.15)



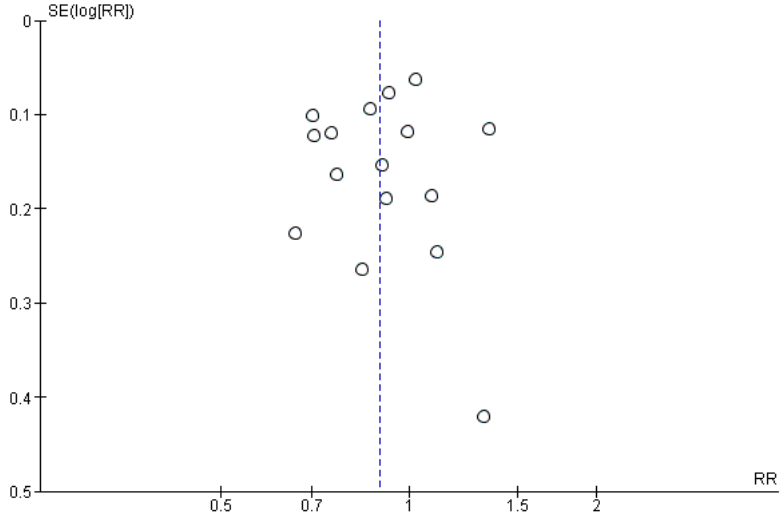
Forest plot of comparison: 1 acamprosat versus placebo, outcome: 1.15 Number of patients lapsed 6-12 month FU.

Figure 11



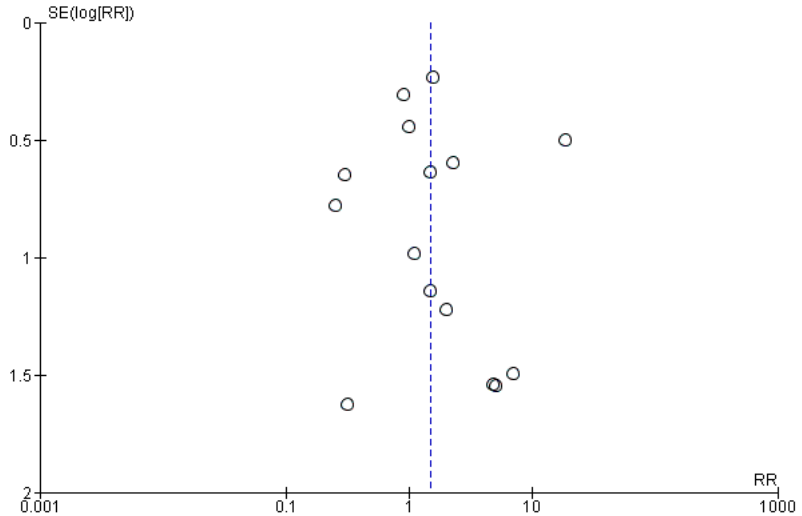
Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Figure 12 (Analysis 1.2)



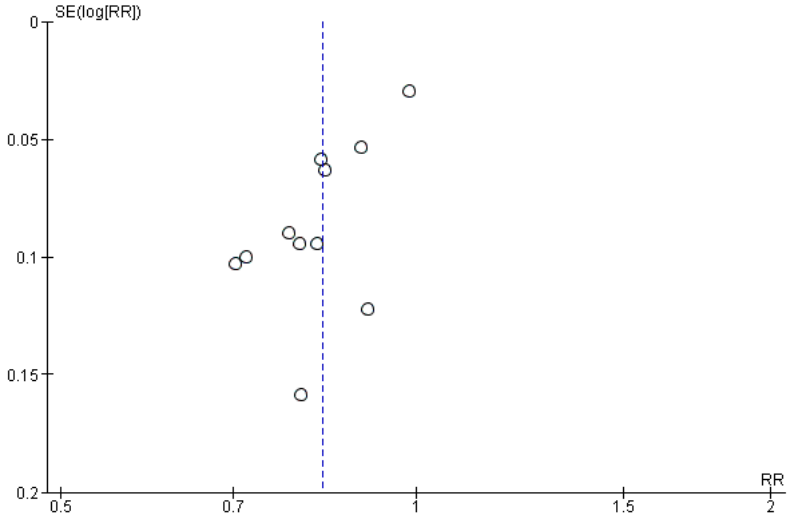
Funnel plot of comparison: 1 acamprosat versus placebo, outcome: 1.2 Dropout all reasons.

Figure 13 (Analysis 1.10)



Funnel plot of comparison: 1 acamprosat versus placebo, outcome: 1.10 Drop-out due to adverse events (EoT).

Figure 14 (Analysis 1.13)



Funnel plot of comparison: 1 acamprosat versus placebo, outcome: 1.13 Number of patients lapsed 6-12 month after baseline.